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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,471	01/30/2004	Michele Cargill	CL1505ORD	6499

37492 7590 06/26/2009

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
06/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/767,471	CARGILL ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,39-46,49-56 and 59-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,39-46,49-56 and 59-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 36, 39-46, 49-56 and 59-90 are pending and examined on the merits.

Please Note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 04/06/2009.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. New grounds of rejection are presented in this Office Action. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **NON-FINAL**.

New Claim Rejection - 35 USC § 112 2nd¶ - Indefiniteness

1. Claim 74 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 74 is unclear over recitation of the phrase 'said T allele or said A allele'. The rejected claim is dependent on claim 74, and claim 74 depends from any of claims 36, 56 or 56. In so far as the rejected claim depends from claim 46, where claim 46 recites properties of a C/C or G/G genotype, there is no antecedent basis for the required T or A alleles.

New Claim Rejection - 35 USC § 112 1st - Written Description, New Matter

2. Claims 73 and 85-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The rejected claims recite the limitation that a provided report is specifically 'in paper form', where the specification as originally filed does not appear to specifically contemplate this particular limitation. Applicants' have not indicated any portion of the specification or any priority documents that provides a basis for this limitation. As such the recited limitation, as specifically requiring a paper form of a report, is considered new matter.

Withdrawn Claim Rejections - 35 USC § 101 - Non statutory subject matter

3. The rejection of claims under 35 U.S.C. 101 as directed to non statutory subject matter, as set forth on pages 4-6 of the Office Action of 11/06/2008, is **WITHDRAWN** in light of the amendments to the claims.

Maintained Claim Rejection - 35 USC § 112 1st¶ - Scope of Enablement modified as necessitated by amendments to the claims

4. Claims 36, 39-46, 49-56 and 59-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification:

While being enabling for:

> A method for identifying a human individual's risk for developing positive autoantibody rheumatoid factor (RF+) rheumatoid arthritis (RA) comprising:

> obtaining a biological sample from said individual wherein the biological sample comprises nucleic acids;
>
> detecting the nucleotide content at position 101 of SEQ ID NO: 36,673 or position 101 of the complement of SEQ ID NO: 36,673, in said nucleic acids;
>
> wherein, detecting the nucleotide T at position 101 of SEQ ID NO: 36,673 , or detecting the nucleotide A at position 101 of the complement of SEQ ID NO: 36,673, identifies the individual as having an increased risk for developing RF+ RA; or wherein detecting the nucleotide C at position 101 of both alleles of SEQ ID NO: 36,673, or detecting the nucleotide G at position 101 of both alleles of the complement of SEQ ID NO: 36,673 identifies the individual as having a decreased risk for developing RF+ RA

does not reasonably provide enablement for diagnostic methods which do not require the detection of particular nucleotide content. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims of the instant application are drawn to methods for identifying an individual who has an altered risk for developing RF+ RA.

The recitation of the steps of the claimed methods do not in fact require the detection of any particular nucleotide content. The claims are drawn to methods steps wherein a nucleic acid is tested for the presence or absence of a SNP, but there is no method step which requires that any particular content is detected or identified in a subject's nucleic acids.

The nature of the invention requires knowledge of an association between a broad variety of nucleic acid content and content that is not required to be detected and altered risk of having RF+ RA.

Direction provided by the specification and working example

The instant specification teaches that an association study of a SNP and a specific disorder involves determining the presence or frequency of the SNP allele in biological samples from individuals with the disorder (i.e. cases) of interest and comparing the information to that of control individuals who do not have the disorder (p.7 ln.25).

The instant specification provides an example of an association study of the polymorphic content at position 101 of SEQ ID NO: 36,673, which may be either a C or a T, and is also identified as hCV16021387 and known in the art as rs2476601. The specification teaches that the frequency of the particular allele was analyzed in two (p.119 lns.6-20) patient populations: a Discovery Set (475 unrelated cases and 475 controls who were RF+); and a Replication Set (840 cases from 463 families and 926 controls). The specification further indicates that various strata (e.g. stratification by sex, age of RA onset, RF+, and number of high or low risk HLA epitopes (p.21)) of each population was also analyzed.

The specification teaches the specific association of the T allele (i.e. a T nucleotide a position 101 of SEQ ID NO: 36,673) with an increased risk of RA as the T allele is found at a significantly higher frequency in the case samples of the Discovery Set and the Replication Set (Table 6; p.121, lns.21-27). It is noted that Table 6 designates the 'A' allele as associated with the increased risk of RA, and the specification indicates that nucleotide content may be described as the reverse complement of the nucleotide content at the position (e.g. p.19, lns.13-19), thus the A

allele of the reverse complement of SEQ ID NO: 36,673 is the T allele of SEQ ID NO: 36,673. The specification does not provide any genotype analysis, and as such it is possible only to conclude that the T allele in either the T/T or C/T genotype is indicative of increased risk of RF+-RA, and C/C genotype is indicative of decreased risk of RF+ RA. The analysis of the Discovery Set is an analysis of RF+ RA, because as stated in the specification all cases of the Discovery Set were RF+. While the instant specification provides that the T allele is indicative of increased risk for RA in the Replication Set, and specifically for the RF+ stratum, the instant specification provides no data for the RF- stratum of the replication set, nor any indication as to how many individuals in the Replication Set were either RF+ or RF-. Thus while the data of specification teaches an association of the T allele with RF+ RA, it is not clear from the specification if the T allele is associated with RF- RA.

The instant specification asserts that since autoimmune diseases share certain similar features that may be due to common genetic factors, SNPs associated with RA may also be used as makers for other autoimmune diseases (p.9, ln.1; p.121, ln.28). However, the instant specification provides no indication of any particular level of association of any SNP with any phenotype other than RA.

The instant specification provides only the association analysis of either C or T content at position 101 of SEQ ID NO: 36,673, and does not provide any analysis of any other polymorphic content at any other position of SEQ ID NO: 36,673.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection of

a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach any association between any polymorphism in SEQ ID NO: 36,673 and altered risk for developing RF+ RA. And because the language of the claims encompass methods wherein the method steps comprise testing for the presence or absence of a SNP, and the methods steps do not in fact required the detection of any specific content, it is relevant to point out the unpredictability in associating any particular SNP with a particular phenotypic trait. For example, Hacker et al teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention in the full scope of the claims. Given that the claims do not recite any step wherein any particular nucleotide content is detected, such experimentation would include examining an association of any nucleotide content with the risk of RF+ RA. This would involve large case:control studies in multiple human populations, and the analysis of different sequence variants. Even if such a large analysis were to be performed, there is no guarantee that one would find any significant

associations beyond those specifically taught in the particular example of the instant specification.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the few specific working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Response to Remarks

Applicants have argued (p. 10 of Remarks of 04/06/2009) that the instant claims have been amended to remove the phrase 'as represented by', and thus are commensurate with the enabled scope. The argument has been considered but is not persuasive to withdraw the rejection. As particularly set forth in the indication of the method enabled by the instant specification, the claims are enabled for methods in which particular nucleotide content is detected and indicative of RF+ RA risk. In the instant case the claims, merely recite methods of 'testing for the presence or absence' of a SNP, and thus do not have a step wherein any particular content is required to be detected.

The rejection as set forth is **MAINTAINED**.

Conclusion

5. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHEN KAPUSHOC whose telephone number is (571)272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634